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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,468	IVERSEN, PATRICK L.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 7-7-04.

Claims 1, 4-6 and 13 are pending in the instant application.

The indication of allowability of claim 13 in the Office action mailed 4-7-04, is hereby withdrawn in light of the new rejection set forth below.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-7-04 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Applicant's arguments, see the communication, filed 7-7-04, pages with respect to the rejection(s)of claim(s) 1, 4-6 and 13 under 103 have been fully considered and are persuasive in part. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the combination of references cited in the new 103 rejection set forth below. In addition, Applicants' arguments, filed 7-7-04, are addressed below as they address the new 103 rejection.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zyskind et al in view of the combination of McKay et al, Summerton, Hudziak et al, Arnold et al, Rothbard et al and Cook.

The claims are drawn to substantially uncharged antisense oligomers which comprise between 10-40 morpholino subunits, specifically targeting the translational start codon for SecA of SEQ ID NO: 2, wherein adjacent subunits are joined by uncharged or charged phosphoramidates or phosphordiamidates, which ratio of uncharged to charged linkages in the oligomers is at least 4:1.

Zyskind et al (USPN 6,228,579, filed 11-14-1997) teach the targeting by antisense oligoncucleotides of the translation initiation region of bacterial mRNA encoding bacterial proliferation genes (see col. 6, lines 1-20), which proliferation genes include E. Coli Sec-A of SEQ ID NO: 2, and which antisense oligonucleotides are effective to hybridize and inhibit the expression of a nucleic acid molecule encoding E. Coli Sec-A of SEQ ID NO: 2, and which inhibition is effective to inhibit bacterial proliferation (see accompanying sequence alignment data). Zyskind et al teach the incorporation of various nucleobase and internucleotide modifications into these antisense oliognucleotides that target bacterial proliferation genes for enhancing the antisense oligonuclelotide's stability from bacterial nucleases and for enhancing the oligonucleotides' ability to target these bacterial proliferation genes (col. 8, line 49- col. 9, line 40). Zyskind et al also teach a SecA dominant lethal clone in example 3 (col. 17-18), and state that "An antisense RNA complementary to SecA mRNA would also be expected to inhibit bacterial proliferation. The nucleotide sequence of such an antisense RNA is shown in FIG. 12." (see col. 18, lines 27-29; see also the accompanying sequence alignment data). Zyskind et al teach the following: "Illustrative embodiments of antisense polynucleotides include polynucleotides having substantial sequence complementarity to the E. coli ... SecA mRNAs, as well as oligonucleotide subfragments thereof, e.g., about 10 to about 100 nucleotides in length, or about 10 to about 60 nucleotides in length, or about 20 to about 50 nucleotides in length... A desired antisense oligonucleotide can be readily identified by preparing and testing overlapping portions of, e.g., an RNA of figs. 1, 2, 4-5 or 12 for antiproliferative effects

as described herein. For example, antisense oligonucleotides about 30 nucleotides in length, each having a 10 nucleotide overlap with adjacent oligonucleotides, can be synthesized and tested for antiproliferative effects." (see col. 9, lines 25-39). (See also col. 5,line 51-col. 6, line 20; col. 8, line 23-col. 9, line 40; col. 13, line 1- col. 18, line 30).

Zyskind does not teach the specific oligonucleotide modicifications comprising morpholino or phorphoramidate groups, nor a minimum ratio of uncharged to charged linkages within the oligonucleotide of 4:1.

McKay et al (USPN6,133,246,4-7-1999) teach antisense targeting various regions of a previously characterized target gene, including preferred targeting of the translational start codon of the target gene of known nucleotide sequence, which antisense comprise morpholino modifications as well as the incorporation of other linkages, both charged and uncharged, as preferred oligonucleotide modifications for enhancing cellular uptake and stability. (See esp. col. 5, line 65-col. 7, line 28; table 1 in col. 36 and table 2 in col. 37).

Summerton (Biochem. Biophys. Acta 1489: 141-158) teaches the incorporation of morpholino groups (comprising between 10-40 morpholino subunits) into antisense oligonucleotides, as well as teaching the advantages of incorporating Rnase-H independent morpholino groups into antisense for enhancing cellular uptake, target binding and bacterial and mammalian nuclease resistance. Summerton also teaches the advantage of targeting the initiation codon region of a target mRNA using Rnase-H independent antisense (see abstract on p. 141; pp. 142-143; figure 2 and text on p. 146; figure 3 and text on p. 147).

Hudziak et al (Antisense and Nucleic Acid Drug Dev. 6: 267-272) teach antisense oligonucleotides comprising between 10-40 morpholino subunits joined by phosphorodiamidate groups, which oligomers had increased resistance to degradation by bacterial and mammalian nucleases (see abstract and introduction on p. 267; Table 1 on p. 268; Table 2 on p. 270; last full paragraph on p. 271).

Arnold et al (USPN 6,060,456 filed 10-27-1997) teach a relationship between incorporating various ratios of uncharged to charged linkages and antisense target binding, antisense stability from bacterial and mammalian nuclease degradation, and enhanced target cellular uptake (penetration), which charged groups include phosphodiesters and phosphorothioates and which uncharged groups include aryl- and alkyl-phosphonates, phosphoramidates and phosphotriesters, as well as alkyl- and aryl-phosphonothioates (see especially col. 2, line 42-col. 4, line 6). Among the charged and uncharged modifications described for enhancing antisense stability include the incorporation of phosphoramidates (e.g. col. 2, line 61-col. 4, line 49).

Rothbard et al (USPN 6,495,663) generally teach methods to enhance oligonucleotide delivery to bacterial cells, and teach the particular difficulty of highly charged oligonucleotides (in the absence of modifications to reduce high charges) in passing across bacterial cellular membranes (see esp. col. 1, line 61-col. 2, line 8).

Cook (USPN 6,239,265, filed 12-9-1998) teach the significance and distinguishing features of various internucleotide linkages (e.g. involving phosphorothioates, methylphosphates, phosphotriesters, phosphoramidates and phosphodiesters), which features includes solubility characteristics imparted to the

oligonucleotides, nuclease resistance, Rnase activating abilities, facilitating cellular uptake and cellular penetration (See especially col. 1, line 36-col. 2, line 14; claims 1-8).

It would have been obvious to one of ordinary skill in the art to utilize antisense oligonucleotides which target and inhibit the expression of E. Coli sec-A, because the polynucleotide sequence of E. Coli sec-A (SEQ ID NO: 2) and the utilization of antisense which target and inhibit the expression of sec-A as an antibacterial agent had been taught previously by Zyskind et al. One of ordinary skill in the art would have been motivated to target particular regions of the target gene of known sequence, including the initiation region, because Zyskind et al teach the targeting of the start codon region of bacterial mRNA encoding bacterial proliferation genes including SEC A of SEQ ID NO: 2, and McKay teaches the general design and testing of antisense oligonucleotides targeting different regions spanning a known target gene, including the initiation region as a preferred target site for antisense, whereby expression of the target gene is obtained. One of ordinary skill in the art would have expected that antisense of at least 10 nucleotides specifically targeting the initiation codon region of SEQ ID NO: 2 would inhibit the expression of SEQ ID NO: 2 in vitro and inhibit bacterial proliferation, as taught previously by Zyskind et al. Targeting the initiation region of a known target gene with antisense of at least 10 nucleotides had been taught by many in the art, including Zyskind for the inhibition of bacterial proliferation genes including Sec-A. It would have been obvious to incorporate stabilizing nucleobase and internucleotide modifications for protecting antisense oligonucleotides from bacterial nuclease degradation because Zyskind et al, Summerton, Hudziak et al, and Arnold et al all teach

means and motivation to incorporate modifications into antisense oligonucleotides to protect the oligonucleotides from bacterial nuclease degradation, including the incorporation of morpholino groups and phosphoramidates. It would have been obvious to one of ordinary skill in the art to incorporate mixed internucleotides linkages, including uncharged and charged linkages, because such mixed linkages had been incorporated into antisense oligonucleotides previously by both Arnold and Cook because a combination of charged and uncharged linkages impart a combination of useful properties for antisense oligonucleotides such as enhanced target binding, stability from nuclease degradation and cellular uptake, which properties have been exploited previously by Zyskind et al, Arnold and Cook. One of ordinary skill would have been motivated to reduce the charges antisense oligonucleotides by incorporating uncharged modifications including phorphoramidates because Rothbard et al teach the motivation to reduce highly charged oligonucleotides to enhance target cell uptake. One of ordinary skill in the art would have been motivated to design antisense oligonucleotides comprising both charged and uncharged oligonucleotides in order to enhance stability, modulate solubility, enhance cellular uptake, target binding. One of ordinary skill in the art would have expected that a ratio within the range of at least 4:1, uncharged to charged linkages would be suitable for enhancing target binding and cellular uptake, because such a range was utilized by Arnold (e.g. see figure 7 and col. 3, line 62-col. 4, line 6 of Arnold). One of ordinary skill would have been motivated to incorporated morpholino phosphoramidate (or phosphordiamidate modifications into antisense because Hudziak et al teach the means and methods for doing so, and one of ordinary

skill in the art would have expected that oligonucleotides comprising these modifications would have enhanced cellular uptake, stability and target binding.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicants' Arguments

Applicant's arguments filed 7-7-04 have been fully considered but they are not fully persuasive. Applicants argue that the teachings of Zyskind et al (USPN 6,228,579) largely provide examples employing plasmid DNA for identifying endogenous microbial proliferation genes, as well as disclosing non-antisense approaches to inhibit bacterial proliferation, and do not teach morpholino group modifications on antisense oliognucleotides - and therefore provide no guidance for a reasonable expectation that the instantly claimed antisense oligonucleotides would enter bacterial cells. Applicants are correct that Zyskind et al provide various examples of the participation of SecA in bacterial proliferation using various techniques that do not explicitly utilize the antisense oligonucleotides claimed. For example, Zyskind et al teach a SecA dominant lethal clone in example 3 (col. 17-18), and state that "An antisense RNA complementary to SecA mRNA would also be expected to inhibit bacterial proliferation. The nucleotide sequence of such an antisense RNA is shown in FIG. 12." (see col. 18, lines 27-29; see also the accompanying sequence alignment data). But, contrary to Applicants' assertions, the examples and teachings provided by Zyskind provide the motivation and means to inhibit SecA expression and inhibit bacterial expression using oligonucleotides

of the size claimed. Zyskind et al, for example, teach the following: "Illustrative embodiments of antisense polynucleotides includes polynucleotides having substantial sequence complementarily to the E. coli ...secA mRNAs, as well as oligonucleotide subfragments thereof, e.g., about 10 to about 100 nucleotides in length, or about 10 to about 60 nucleotides in length, or about 20 to about 50 nucleotides in length... A desired antisense oligonucleotide can be readily identified by preparing and testing overlapping portions of, e.g., an RNA of figs. 1, 2, 4-5 or 12 for antiproliferative effects as described herein. For example, antisense oligonucleotides about 30 nucleotides in length, each having a 10 nucleotide overlap with adjacent oligonucleotides, can be synthesized and tested for antiproliferative effects." (see col. 9, lines 25-39).

Applicants assert that no reasonable expectation that the instantly claimed oligonucleotides would successfully enter bacterial cells has been provided by Zyskind, especially since Zyskind et al do not explicitly teach morpholino modifications of antisense oligonucleotides. Applicants are correct that Zyskind do not disclose morpholino groups. But Zyskind is correctly relied upon as one of several references in the instant obvious rejection, and disclose the means and motivation for modifying antisense oligonucleotides for enhancing bacterial cell uptake and stability (see especially col. 8, line 66-col. 9, line 24). These teachings, combined with the teachings of Agrawal, Hudziak, Cook, Summerton, Rothbard, McKay and Arnold, provide both the means and the motivation that render claims 1 and 4-6 obvious.

Applicants argue that McKay et al do not teach anything pertaining to bacterial proteins or the use of antisense to inhibit bacterial growth, nor do they provide any clear

guidance towards the use of substantially uncharged morpholino antisense oligomers. Applicants are correct that McKay et al do not teach bacterial protein targeting (and subsequent bacterial growth inhibition) using antisense. McKay et al is cited in the instant rejection for its teachings of the general applicability of antisense targeting and inhibition of a known target gene. The use of antisense targeting and inhibition in vitro were routine in the art at the time the instant invention was made, as well illustrated by McKay. The techniques taught by McKay are applicable to other target genes, and are not restricted to the Jun N-terminal kinase gene explicitly disclosed by McKay. Furthermore, McKay et al teach the targeting of the initiation codon of a target gene as one of the preferred sites of antisense targeting for inhibition of expression, as well as teaching the incorporation of morpholino groups, as well as the incorporation of other linkages, both charged and uncharged, as preferred oligonucleotide modifications for enhancing cellular uptake and stability. These modifications were well known in the art and their incorporation into antisense was considered routine in the art at the time the instant invention was claimed, as evidenced by the teachings of McKay et al.

Applicants also argue that Arnold et al teach away from the instant invention because the chimeric antisense oligonucleotides described by Arnold et al contain RNase-H activating regions, while the morpholino oligomers, according to Applicants, are considered RNase H inactive. Applicants are correct that Arnold et al teach chimeric antisense constructs comprising both RNase activating and RNase inactive regions. But, contrary to Applicants' assertions, Arnold et al does not teach away from the instant invention. Arnold et al teach the suitability of phosphodiester (e.g. charged)

linkages for activation of Rnase-H (see col. 2, lines 42-60), but within the general context of oligonucleotide stability and target binding: "While phosphodiester linkages, being charged, are suitable to allow activation of RNAseH, they suffer from the disadvantage of being subject to degradation by naturally occurring endo- and/or exonucleases. A variety of alternative linkage groups, some of which are nuclease-resistant, have been developed or proposed for use with antisense compounds." (col. 2, lines 61-67). Within the larger context of satisfying target binding, target specificity, Rnase activation and antisense stability from degradation, Arnold et al then describe the various modifications that may be introduced into the various regions of chimeric oligonucleotides, both in the regions of Rnase activation, and in the flanking non-activating regions (e.g. see col. 2, line 61-col. 4, line 49). Among the charged and uncharged modifications described for enhancing antisense stability include the incorporation of phosphoramidates (e.g. col. 2, line 61-col. 4, line 49). Therefore, rather than teaching away from the instantly claimed invention, Arnold et al provide the motivation to incorporate phosphoramidates into antisense oligonucleotides.

Applicants argue that Cook et al is directed to the preparation of oligonucleotides with chiral purity and does not teach morpholino containing oligomers. Applicants are correct that Cook et al teach the means and motivation for incorporating phorphoramidates into antisense oligonucleotides, which when combined with the other references cited, render the instant invention obvious to one of ordinary skill in the art.

Allowable Subject Matter

SEQ ID NO: 47 appears free of the prior art searched and of record.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
9-22-04

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